SCIENTIFIC DISCUSSION

This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	[HA712 trade name] *
Manufacturer of Prequalified Product:	Celltrion Pharm Inc 82, 2 Sandan-ro Ochang-eup Cheongwon-gu Cheongju-si Chungcheongbuk-do 28117 Republic of Korea
Active Pharmaceutical Ingredient (API):	Lamivudine/Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Codes):	Antivirals for treatment of HIV infections, combinations (lamivudine, tenofovir disoproxil fumarate: J05AR12)
Therapeutic indication:	[HA712 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in patients weighing at least 30 kg or more

1. Introduction

[HA712 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in patients weighing at least 30 kg or more
[HA712 trade name] should be initiated by a health care provider experienced in the management of HIV infection.

2 Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part.*

Active pharmaceutical Ingredients (APIs)

Lamivudine and Tenofovir disoproxil fumarate have been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the APIs, used in the manufacture of [HA712 trade name], are of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, croscarmellose sodium, magnesium stearate, Cellactose®80 (powdered cellulose and lactose monohydrate) and colloidal silicon dioxide. Cellactose®80 is in-house controlled, while the other excipients conform to compendial requirements. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide and macrogol/polyethylene glycol. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white oblong shaped, biconvex film coated tablet debossed with 'C' and '0' on one side and plain on the other side. The tablets are presented in white opaque HDPE bottles, each with a silica gel packet and closed with polypropylene child resistant closure with heat seal liner

The goal of the development was to formulate an immediate release FDC dosage form, which is stable and bioequivalent to the individual WHO comparator products Epivir® (Lamivudine 300mg) Tablets and Viread® (Tenofovir disoproxil fumarate 300mg) Tablets. The excipients were selected based on the excipients used for the comparator products and API-excipient compatibility studies. Dry granulation was selected to improve flowability of the APIs and to mitigate risk for hydrolysis of tenofovir disoproxil fumarate API. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification of the APIs (TLC, HPLC) and colorant, dissolution (HPLC detection), uniformity of dosage units (content uniformity by HPLC), assay (HPLC), related substances (HPLC), residual solvent (ethanol, GC), water determination (KF), and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The data showed some degradation for the water sensitive tenofovir disoproxil fumarate at the accelerated condition, though no significant change was observed and the results for all parameters at this storage condition were within agreed acceptance criteria. Based on the available stability data, the proposed shelf-life and storage conditions of the unopened bottles as stated in the SmPC are acceptable. The in-use storage period after first opening of the bottle of pack size of 100 tablets is based on in-use stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bio-Equivalence

The following bioequivalence study has been performed in 2017 according to internationally accepted guidelines.

A single center, single-dose, open-label, laboratory-blinded, randomized, two-treatment, two-period crossover study to determine the bioequivalence of a new fixed dose combination film-coated tablet formulation containing 300 mg Tenofovir Disoproxil Fumarate and 300 mg lamivudine against Viread® film-coated tablets containing 300 mg Tenofovir Disoproxil Fumarate and Epivir® film-coated tablets containing 300 mg Lamivudine in at least 40 healthy males and females under fasting conditions (study no. PXL231461 / CT-G02 1.2).

The objective of the study was to compare the bioavailability of the stated Lamivudine/Tenofovir disoproxil fumarate 300mg/300 mg FDC tablet manufactured by/for Celltrion Inc., Republic of Korea (test drug) with the reference formulations Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 tablet Lamivudine/Tenofovir disoproxil fumarate 300mg/300mg (lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) Batch no. CBAU002.

Treatment R: Reference
– 1 tablet Epivir®
(lamivudine 300 mg)
Batch no. 5ZP1465.
– 1 tablet Viread®
(tenofovir disoproxil fumarate 300 mg)
Batch no. 007657.

A 7 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 18 samples within 48h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for lamivudine and tenofovir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 40 ng/ml for lamivudine and 4.7 ng/ml for tenofovir.

The study was performed with 48 participants; data generated from a total of 47 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for lamivudine and tenofovir as well as statistical results are summarised in the following tables:

Lamivudine

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)#	1.35 ± 0.47	1.23 ± 0.43	-	-
C_{max} (ng/ml)	2680 ± 640 (2602)	2671 ± 786 (2570)	101.4	96.1 – 107.1
AUC_{0-t} (ng.h/ml)	10950 ± 2569 (10671)	11050 ± 2612 (10763)	99.2	94.5 – 104.0
AUC_{0-inf} (ng.h/ml)	11240 ± 2557 (10975)	11370 ± 2586 (11096)	98.9	94.5 – 103.6

* geometric mean

Tenofovir

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)#	1.08 ± 0.41	0.87 ± 0.36	-	-
C_{max} (ng/ml)	290 ± 80 (279)	314 ± 89 (303)	92.0	87.0 – 97.3
AUC_{0-t} (ng.h/ml)	1940 ± 522 (1871)	1971 ± 473 (1920)	97.5	93.6 – 101.4
AUC_{0-inf} (ng.h/ml)	2191 ± 604 (2111)	2224 ± 556 (2161)	97.7	93.7 – 101.8

* geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding lamivudine and tenofovir. Accordingly, the test Lamivudine/Tenofovir disoproxil fumarate 300mg/300 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Inc.).

4. Summary of Product Safety and Efficacy

[HA712 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [HA712 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products, Viread® 300mg Tablets and Epivir® 300 mg Film-Coated Tablets for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [HA712 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA712 trade name] has shown to be bioequivalent with Viread® 300mg Tablets, Gilead Sciences, Inc. and Epivir® 300 mg Film-Coated Tablets, GlaxoSmithKline.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA712 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA712 trade name] was acceptable for the following indication: “in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in patients weighing at least 30 kg or more”, and

has advised that the quality, efficacy and safety of [HA712 trade name] allow inclusion of [HA712 trade name], manufactured at Celltrion Pharm Inc, 82, 2 Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do 28117, Republic of Korea, in the list of prequalified medicinal products.